**Atlas of Genetics and Cytogenetics in Oncology and Haematology**

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# Deep Insight Section

## Genomic Imprinting: Parental differentiation of the genome

**J Keith Killian**

National Institutes of Health, National Cancer Institute, Laboratory of Pathology, Bldg. 10 Room 2N212, Bethesda, MD 20892, USA (JKK)

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### *Overview: a mark about parental origin*

Genomic imprinting is the biological process whereby a gene or genomic domain exists in a state of epigenetic differentiation that depends upon its parent of origin. Importantly, the establishment and propagation of these parent-specific genomic conformations does not alter the primary DNA sequence comprised of A, C, G, and T nucleotides. Genomic imprints may be covalent (DNA methylation) or non-covalent (DNA-protein and DNA-RNA interactions, genomic localization in nuclear space), and the process of imprinting encompasses the specialized nuclear enzymatic machinery that maintains parental epigenetic markings throughout the cell cycle. Because of genomic imprinting, the parent of origin of homologous genetic alleles in diploid individuals can be determined in the absence of DNA sequence polymorphisms and without recourse to parental DNA samples. As illustrated in Figure 1, alleles of imprinted genes look and behave differently, as determined by parent of origin.

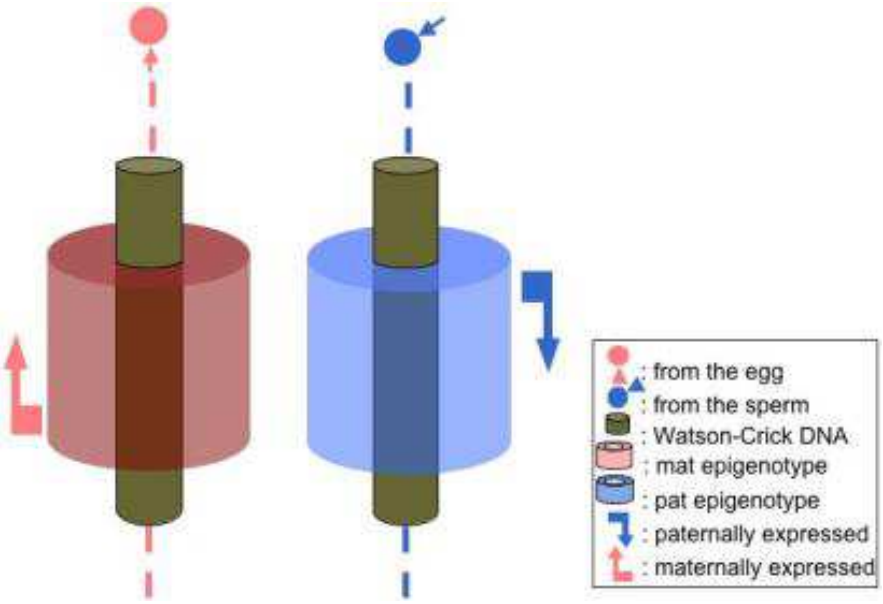



Figure 1: Genomic imprinting results in parent-specific epigenetic differentiation and monoallelic gene expression. Parental imprints are established during gametogenesis as homologous DNA passes uniquely through sperm or egg; subsequently during embryogenesis and into adulthood, alleles of imprinted genes are maintained in two "conformational"/epigenetic states: paternal or maternal. The gamete-specific epigenotypes observed in egg and sperm may go through metamorphosis during embryogenesis into their somatic forms.

While Gregor Mendel did not provide details of the anatomy of genes, a fundamental tenet of Mendelian principles of inheritance is that a gene's parent of origin does not influence its dominance or recessiveness in phenotype determination. However, in sexually reproductive organisms including plants, insects, invertebrates, and chordates, the parental origin of genetic alleles often determines their fates. Mammals have diverged from other sexually reproductive organisms through the imprinting of a distinct family of genes involved in embryogenesis. For these imprinted genes, the diploid offspring distinguishes between maternally-inherited and paternally-inherited alleles, and selectively expresses only one of them while inactivating the other. Allelic parental discrimination and silencing at imprinted loci is imperative in the procreation of wild type mammalian progeny. The life history of these genes- including when in the past, why, and how they became imprinted- remains a mystery which fascinates evolutionary and developmental biologists, as well as clinicians seeking answers and remedies for "non-Mendelian" inherited human genetic disorders. Most studies of mammalian imprinting have investigated the phenomenon in mice or humans, but recent studies of a wide variety of mammals, including monotreme (egg-laying), marsupial (altricial offspring carried in a pouch), and eutherian ("placental") mammals are helping unravel the origins and mechanisms of the unique family of imprinted genes. Recent focus on the physical structure and biochemisty of imprinted chromatin domains also is providing an image of parental differentiation within the genome. The historical recognition, evolution, physical chromatin basis, and pathologic consequences of parental genomic imprinting will be reviewed in this article.

## Historical discovery of parental genomic differences

An ancient puzzle for naturalists was the observation that parthenogenetic reproduction-asexual female reproduction- occurs naturally in many vertebrates such as birds and fishes but not mammals. However, in 1937 the renowned reproductive biologist and endocrinologist Gregory Pincus reported that he had successfully achieved "fatherless rabbits" via parthenogenesis. Such reports of parthenogenesis discount the need for sperm or male contributions to reproduction.

Partly attributable to Pincus' parthenogenetic rabbit, and the powerful dual influences of Gregor Mendel's laws of genetic inheritance and the Watson-Crick model of the DNA double helix, epigenetic memory and inheritance were not initially widely recognized. That genes could exist in parent-specific conformations, and that these conformations could be self-templating from one cell division to the next, simply was not a mainstream viewpoint until recently.

Following the initial report of successful parthenogenesis in rabbits, early experimental attempts by developmental biologists to produce parthenogenetic mice consistently failed to develop normally, but the "embryoids" did show various degrees of development and differentiation along embryonic lineages. It was therefore believed that successful parthenogenesis was more a matter of technical optimization of the procedure, and a fundamental need for sperm-derived nuclear genome is even discounted in some reports. Instead, the possible explanations included: asynchrony between the parthenogenone developmental stage and the uterine lining at the time of implantation; alterned nucleus:cytoplasmic ratio; failure due to absence of a sperm cytoplasmic factor; the expression of recessive lethal mutations; an incomplete zona reaction; or gene dosage effect related to X-chromosome imbalance (Graham, 1974).

In parallel with such deliberate experimental manipulations to improve failing parthenogenesis attempts in mice, human pathologists were serendipitously approaching an explanation for failed mammalian parthenogenesis from a different realm of investigation, namely female germ cell tumors. Pathologic analysis of two peculiar human germ cell tumors provided the conceptual breakthrough for recognizing the fundamental functional difference between the maternal and paternal genomes during cell growth and differentiation (Linder et al., 1975; Kajii and Ohama, 1977; Wake et al., 1978). The histopathologic phenotype of ovarian teratomas reveals well-differentiated fetal structures of all three germinative layers (ectoderm, mesoderm, endoderm), while the hydatidiform mole contains no such elements, only extra-embryonic trophoblast elements. Both of these tumors arise from ovarian germ cells, and typically have a 46,XX normal karyotype. However, the teratoma is gynogenetic in origin (Figure 2) while the hydatidiform mole is androgenetic (Figure 3). Thus, as recognized in the mid 1970's, the developmental potential of ovarian germ cells is determined by the parental origin of the genome driving its development, indicating a fundamental distinction between the nuclear genomes of sperm and egg. Further analyses of pathologic specimenes ruled out a contributory role for parental origin of mitochondrial DNA or cytoplasmic factors in the differentiation of germ cell tumors.

PARTHENOGENIC ORIGIN OF TERATOMAS — LINDER ET AL.

THE NEW ENGLAND JOURNAL OF MEDICINE Jan. 9, 1975

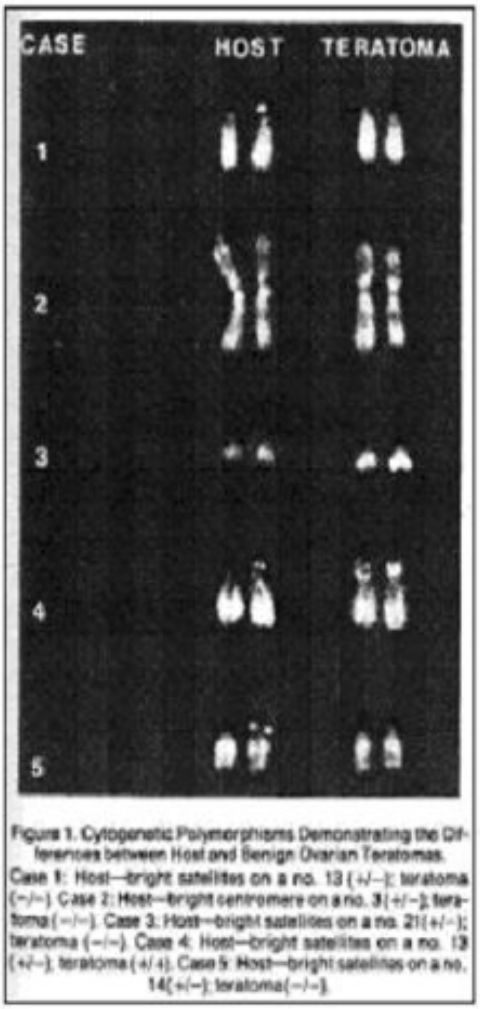



Figure 1. Cytogenetic Polymorphisms Demonstrating the Differences between Host and Benign Ovarian Teratomas.
Case 1: Host—bright satellites on a no. 13 (+/−); teratoma (−/−). Case 2: Host—bright centromere on a no. 3 (+/−); teratoma (−/−). Case 3: Host—bright satellites on a no. 21 (+/−); teratoma (−/−). Case 4: Host—bright satellites on a no. 13 (+/−); teratoma (+/+). Case 5: Host—bright satellites on a no. 14 (+/−); teratoma (−/−).

Table 1. Comparison of Chromosomal Polymorphisms in Normal Tissues to Teratomas.

| Case No. | Tissue* | 1 | 3 | 4 | 13 | 14 | 15 | 21 | 22 | Hetero-zygous | Homo-zygous |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | N | +/− | | +/− | +/− | | +/− | | +/− | 5 | |
| | T | −/− | | −/− | −/− | | +/+ | | +/+ | | 5 |
| 2 | N | | +/− | | | | | | | 1 | |
| | T | | −/− | | | | | | | | 1 |
| 3 | N | | | | +/− | +/− | | +/− | | 3 | |
| | T | | | | −/− | +/+ | | −/− | | | 3 |
| 4 | N | | +/− | | +/− | | +/− | +/− | | 4 | |
| | T | | +/+ | | +/+ | | +/+ | +/+ | | | 4 |
| 5 | N | | +/− | | +/− | +/− | +/− | | | 4 | |
| | T | | +/+ | | +/+ | −/− | −/− | | | | 4 |
| Total no. | | 1 | 3 | 1 | 4 | 2 | 3 | 2 | 1 | 17 | 17 |

*N denotes normal, T teratoma.
†No heterozygosity was found for chromosomes 9 & 16.

Table 2. Comparison of Electrophoretic Polymorphisms in Normal Tissues as Compared to Teratomas.

| Case No. | Tissue | Phenotype* PGM$_1$ | PGM$_3$ | PGD |
|---|---|---|---|---|
| 1 | Normal | 2-1 | 1 | A |
| | Tumor | 1 | 1 | A |
| 2 | Normal | 2-1 | 2-1 | A |
| | Tumor | 2 | 1 | A |
| 3 | Normal | 1 | 2-1 | A |
| | Tumor | 1 | 2-1 | A |
| 4 | Normal | 1 | 1 | AB |
| | Tumor | 1 | 1 | AB |
| 5 | Normal | 2-1 | 1 | A |
| | Tumor | 2-1 | 1 | A |

*PGM$_1$ denotes phosphoglucomutase 1, PGM$_3$ phosphoglucomutase 3, & PGD 6-phosphogluconic dehydrogenase.

Figure 2 : Chromosomal studies of tri-embryo-lineage (endoderm, mesoderm, ectoderm) teratomas reveal a uniquely gynogenetic constitution.

As discussed by Wake, Takagi, and Sasaki (J Natl Cancer Inst, 1978):
"In contrast to androgenetic ova producing only hydropic villi, parthenogenetic oocytes in the ovary produce several mature tissues. Remarkable differences in the end products of both types of conceptuses are of special interest with regard to the possible physiologic difference between maternally and paternally derived genome in the egg cytoplasm, influence of implantation site (ovary versus uterus), and interaction between mother and conceptus in early mammalian embryogenesis. Parthenogenetic or gynogenetic conceptuses developing in uteri, if existent, would help resolve these problems."

As pointed out by Wake et al., analysis of human tumors could not control for potential effects of local environment in guiding developmental programming, for the teratomas develop with the ovary while hydatidiform moles develop in utero following passage through the oviduct; furthermore, various endocrinologic and developmental parameters obviously cannot be controlled for when studying human pathologic specimens. Nevertheless, pathologic human germ cell tumor analysis provided an early conceptual framework in the recognition of the different agendas of paternal versus maternal genomes during development.

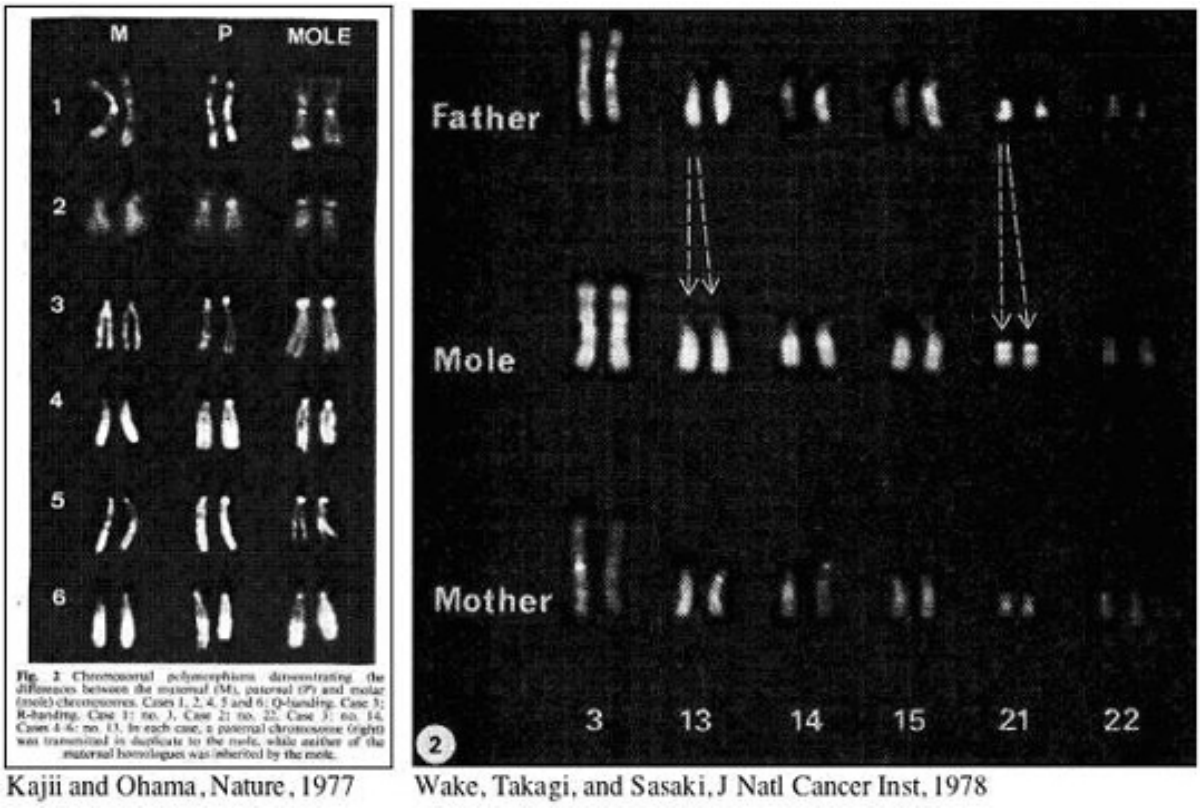
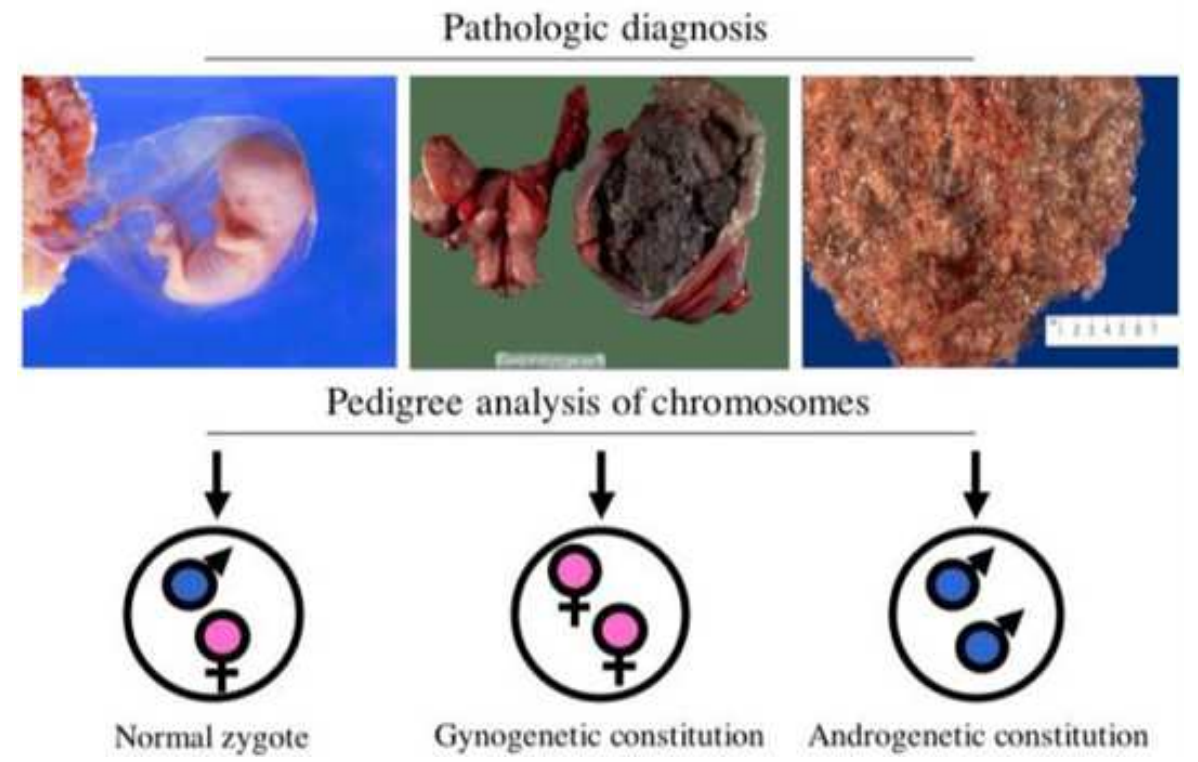



Figure 3 : Chromosomal studies of mono-extraembryonic-lineage (trophoblast) hydatidiform moles reveal a uniquely androgenetic constitution.



## Mouse pronuclear transplantation studies

Further mouse parthenogenesis and androgenesis experiments of the early 1980's provided functional evidence of heritable differences between the maternal and paternal programming of their germ cell genomes while controlling for many potential confounding factors. The pronuclear transplantation studies by McGrath and Solter (McGrath and Solter, 1984) and Surani and colleagues (Surani et al., 1984) provided the requisite parthenogenetic/gynogenetic conceptuses developing in uteri referred to by Wake et al. The series of pronuclear transplantation experiments directly confirmed that male and female parent-derived genomes direct fundamentally different developmental programs in developing embryos. In these experiments, a mature oocyte is devoided of its pronucleus while leaving the cytoplasm along with the mitochondria and other organelles intact; then this empty egg is reconstituted with either one sperm and one oocyte pronucleus (normal complement), two sperm pronuclei and no oocyte pronucleus (androgenetic complement), or two oocyte pronuclei and no sperm pronuclei (gynogenetic complement). After intrauterine implantation of the embryo or embryoids in pseudo pregnant mice, they differentially develop along lines remarkably homologous to the germ cell tumors in humans according to parental origin of nuclear genome (Figure 5).

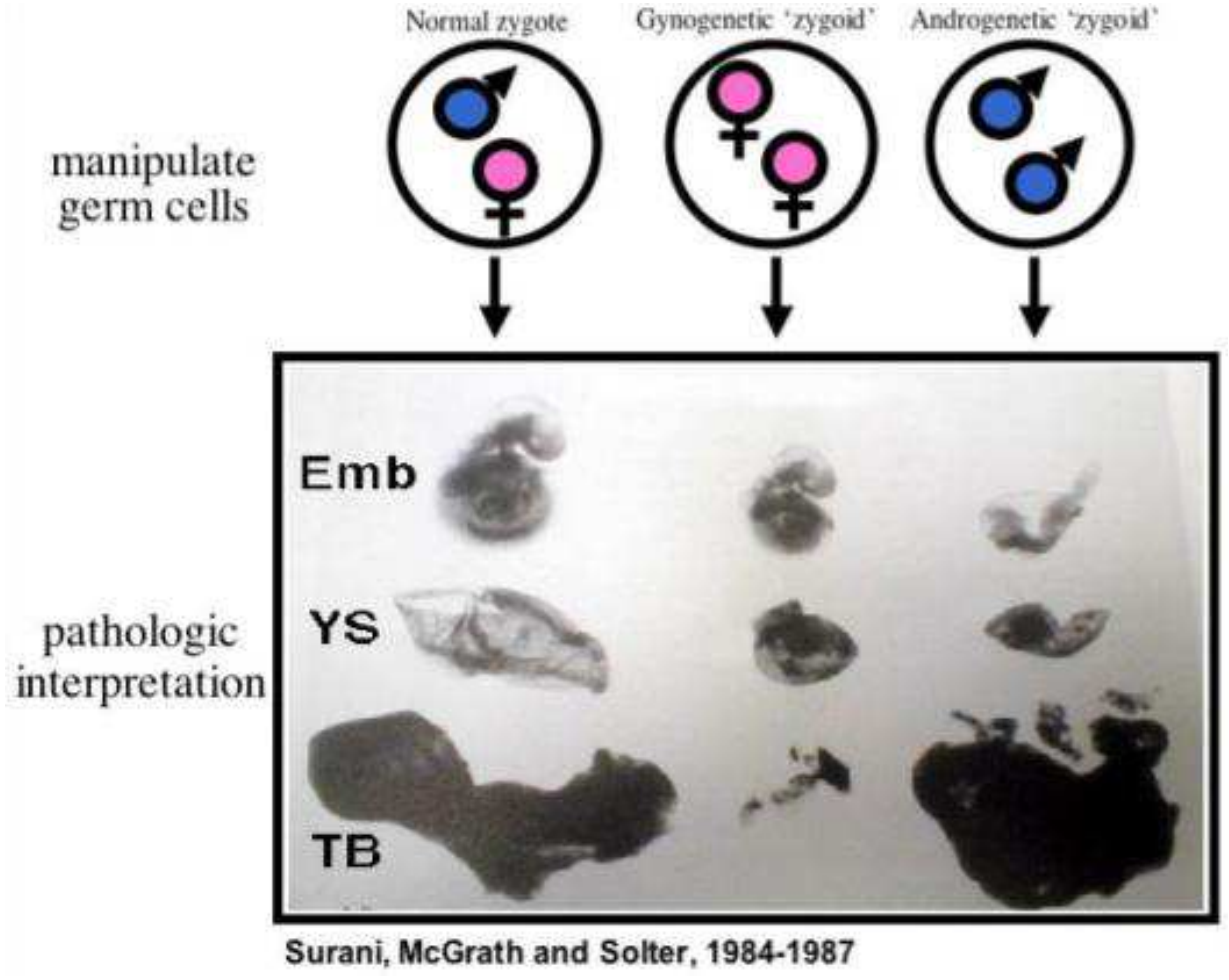



Figure 5 : Mouse germ cell pronuclear transplant experiments convincingly demonstrate a different agenda for sperm- versus egg-derived nuclear genomes during development. Development in the absence of a sperm-derived genome (middle column) shows fairly good development of the embryo proper but failed development of the trophoblast lineage. Development in the absence of an egg-derived genome (right column) shows failed development of the embryo proper but exuberant trophoblast growth. Figure by permission, Nature.

## First recognized human clinical syndromes related to genomic imprinting

### Clinical diseases

Following neoplastic teratoma and hydatidiform mole, the first human clinical syndromes recognized to result from imprinted loci were Prader-Willi syndrome and Angelman syndrome as reported in 1989 (Nicholls et al., 1989). These studies revealed that identical genetic deletions as well as uniparental disomy for a domain on 15q resulted in markedly different clinical phenotypes depending on the parental origin of the deletion/disomy.

## First identified specific imprinted genes

The idea that maternally-and paternally-derived alleles of certain genes function differently in the cell was further confirmed when the first distinct imprinted genes were identified. These were the genes coding for insulin like growth factor 2 (IGF2) and for its receptor, the mannose 6-phosphate/IGF2 receptor (M6P/IGF2R) (Barlow et al., 1991; Dechiara et al., 1991). IGF2 is a critical fetal growth factor, while the M6P/IGF2R targets IGF2 for degradation and therefore suppresses fetal growth. Heterozygous mice that harbor null alleles of these genes have different phenotypes,

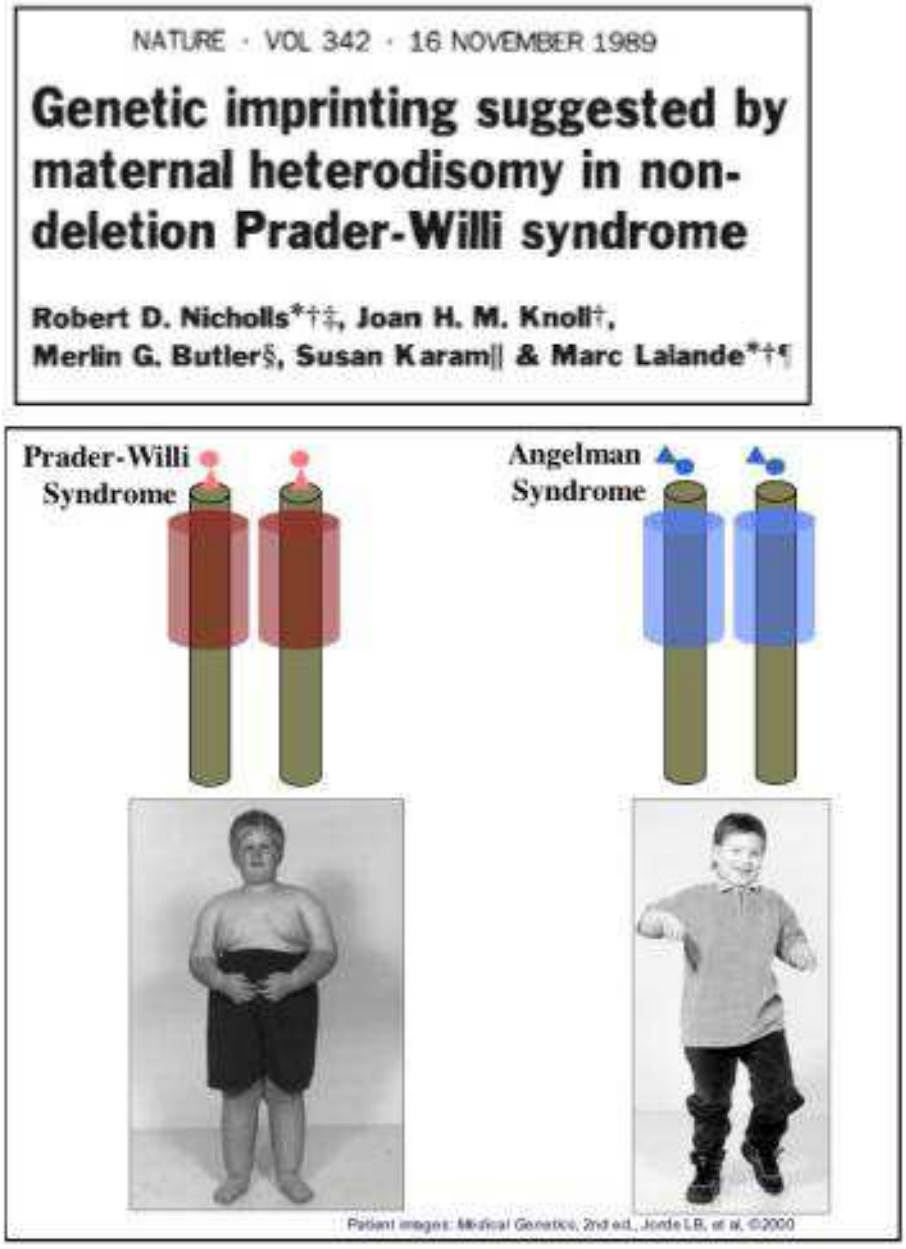



Figure 6: Recognition of imprinted inheritance of Prader-Willi and Angelman syndromes. Nicholls et al. reasoned that parentally imprinted gene(s) reside in human 15q11-13.

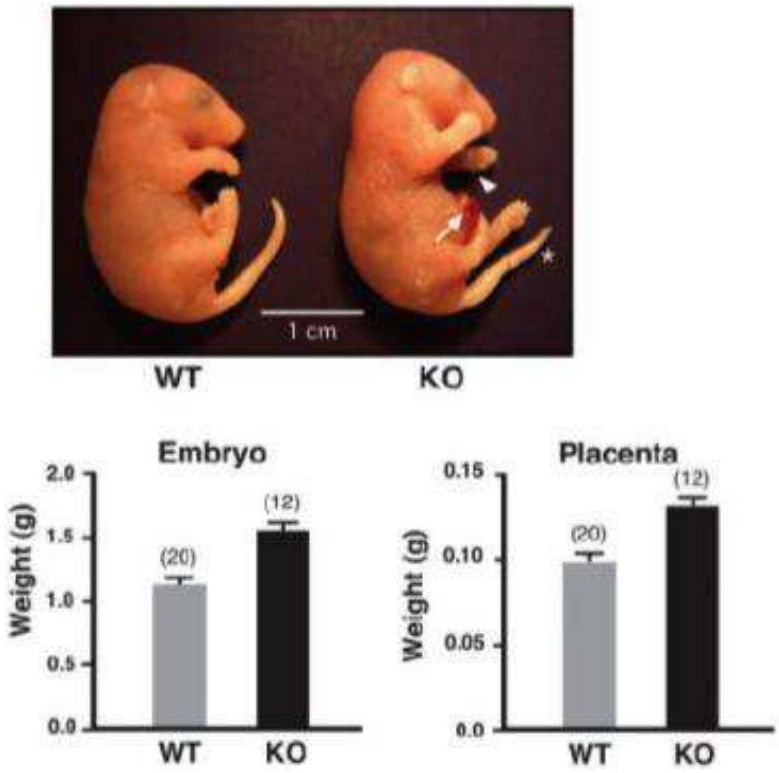



Figure 7: A mutant maternally-derived allele of Igf2r results in a malformed mouse embryo with placental overgrowth. Image from Wylie et al., AJP, 2003.

depending on the sex of the parent from which they inherited the null allele. Genetic and molecular analyses in mice showed that IGF2 is expressed uniquely from the paternally-inherited allele, while M6P/IGF2R is expressed from the maternally-inherited allele.

The monoallelic expression of these and other imprinted genes, in a parent-of-origin-dependent manner, differs from the post-zygotic monoallelic expression of certain genes involved in olfaction and immunity. At present, some 4 score genes are known to be imprinted, and it is estimated that mammalian genomes may contain several hundred imprinted genes in total (Luedi PP et al., 2005.). In addition to identifying and validating the various imprinted genes, a major focus of current research in this field is to understand how and why some alleles "remember" their parental lineage long after pronuclear fusion in the zygote, while the majority of alleles "forget" from which parent they were inherited. This entails dissecting the unique physical chromatin structure and epigenetic DNA modifications, as well as the enzymatic processes that propagate them.

The relative diminished expression from one parental locus is sufficient to create a pathologic phenotype in heterozygous mutant animals in which the imprint gene null allele is inherited through the dominant/expressing parent. Similarly, in human uniparental disomies that encompass imprinted loci, diminished expression from imprinted loci is often syndromic. In fact, one strategy for identifying imprinted genes is based upon UPD genotype-phenotype correlations.

Thus, the diminished gene expression from the stifled parental allele is biologically insufficient to support a healthy phenotype, and imprinted gene mutations are usually dominant when they affect the expressed allele. Feedback regulation of transcription at imprinted loci does not allow sufficient upregulation of transcription from the silenced allele, and organisms do not have recourse to the silenced otherwise wild-type allele in the event that the expressed allele is null.

Clinical human diseases and syndromes stemming from the unique vulnerabilities of imprinted loci include : gestational trophoblastic disease, teratomas, Beckwith-Wiedemann syndrome, Prader-Willi syndrome, Angelman syndrome, Silver-Russell syndrome, transient neonatal diabetes, social-cognitive defects in Turner syndrome, and multiple neoplasias associated with loss of imprinting at oncogene loci. OMIM (On-line Mendelian (!) Inheritance in Man) database of the NCBI (United States National Center for Biotechnology Information) contains detailed entries on many imprinted genes and syndromes.

In summary therefore, a mammalian individual's DNA contains information about the parental origin of numerous genes and, for these parentally-differentiated loci, improper balancing of allelic sex may have pathological effects.

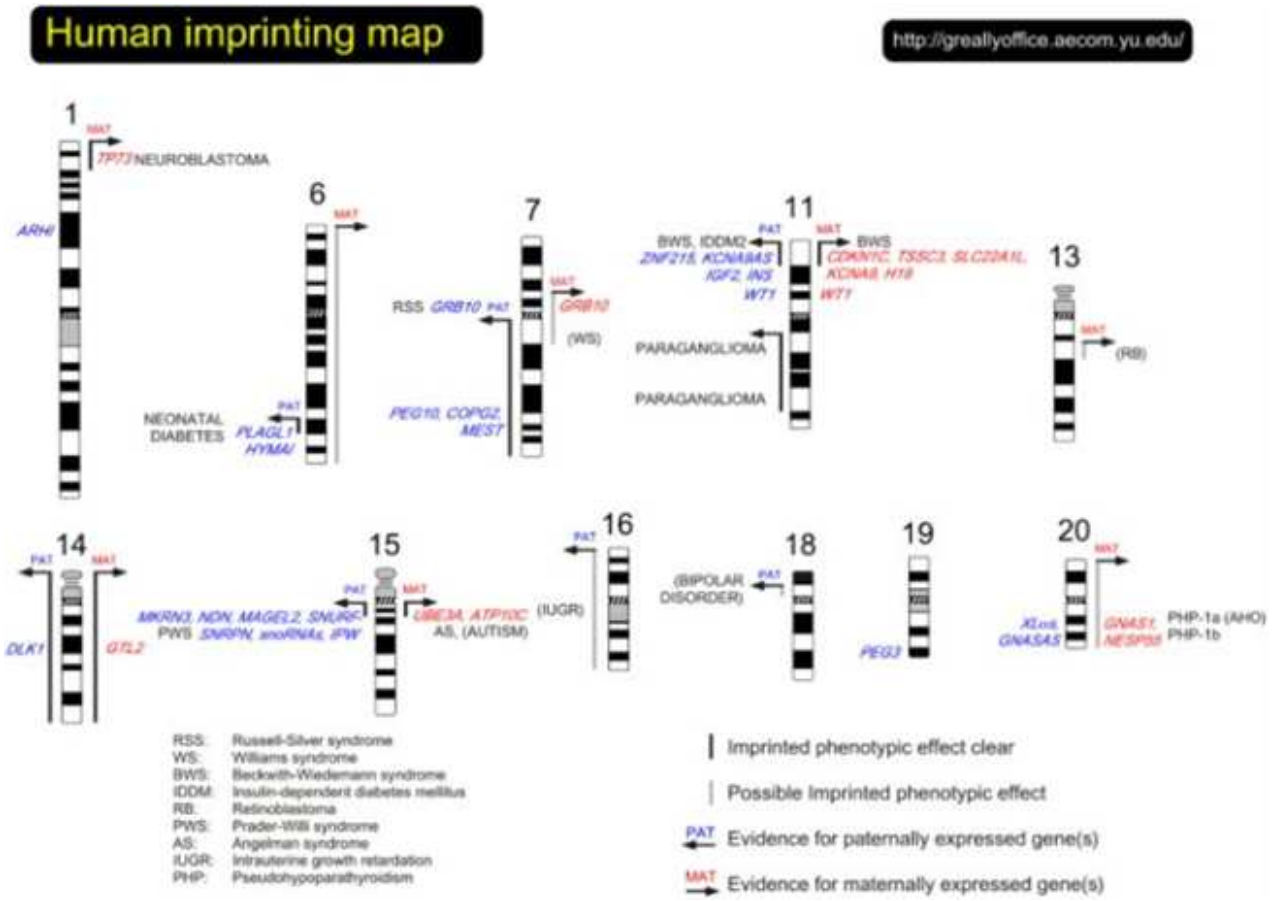



Figure 8. Human imprinting map, showing genomic distribution of known imprinted genes and clinical syndromes. Figure from http://greallyoffice.aecom.yu.edu/.

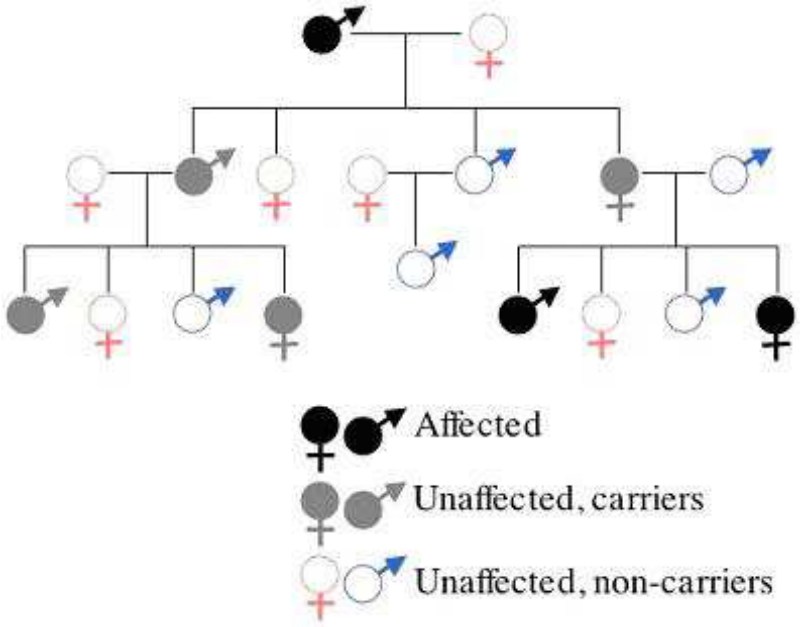



Figure 9: Pedigree of imprinted maternally expressed phenotype. The phenotype is expressed only when the mutant allele is inherited from the mother. Thus, mutant imprinted alleles can remain masked when they are paternally inherited, but clinically re-appear in one-half of children of carrier daughters.

## Physical examination of imprinted chromosome domains

Epigenetic programming loosely refers to any modification to DNA that is imposed after DNA polymerase assembles the primary DNA sequence. Heritable epigenetic modifiers include physical as well as spatio-temporal programming of DNA, and candidate epigenetic markings capable of gene imprinting include cytosine methylation (Reik et al., 1987; Mayer et al., 2000; Figure 10), histone acetylation and other modifications, replication timing asynchrony, chromatin structure and nuclear localization. Molecular dissection of the Prader-Willi/Angelman syndrome imprinted domain on 15q provides a good example of the physical epigenetic modifications that can regulate an imprinted domain (reviewed by Soejima and Wagstaff, 2005; Figures 11 and 12).

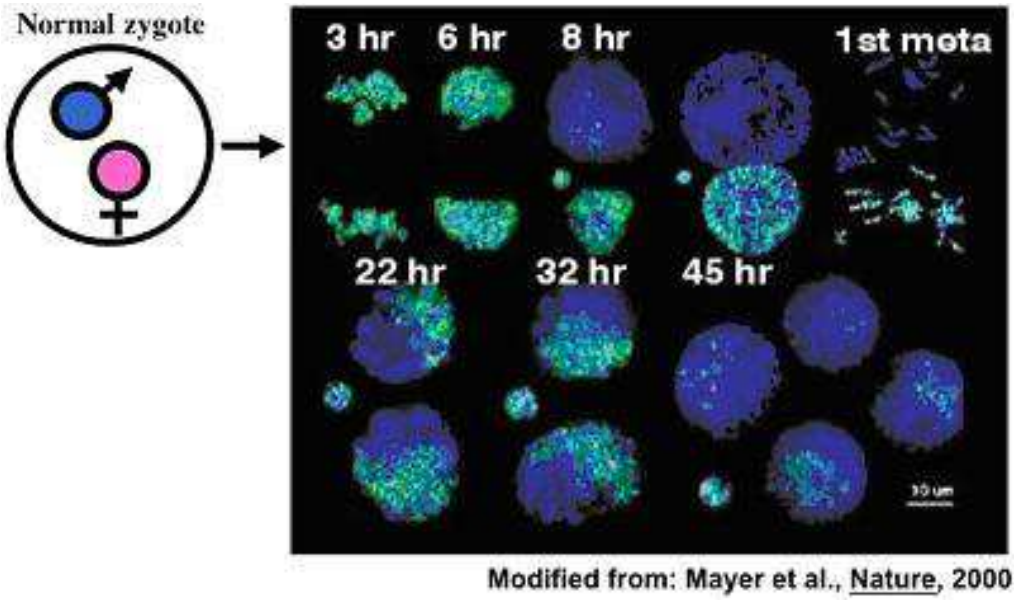



Figure 10: Immunostaining for 5-methyl cytosine in zygotes reveals a remarkable global methylation differentiation between the maternally- versus paternally-inherited chromosomes following fertilization. In particular, the paternally inherited chromosomes appear nearly completely demethylated beginning 6-8 hours after fertilization, while the maternal chomosome methylation persists.

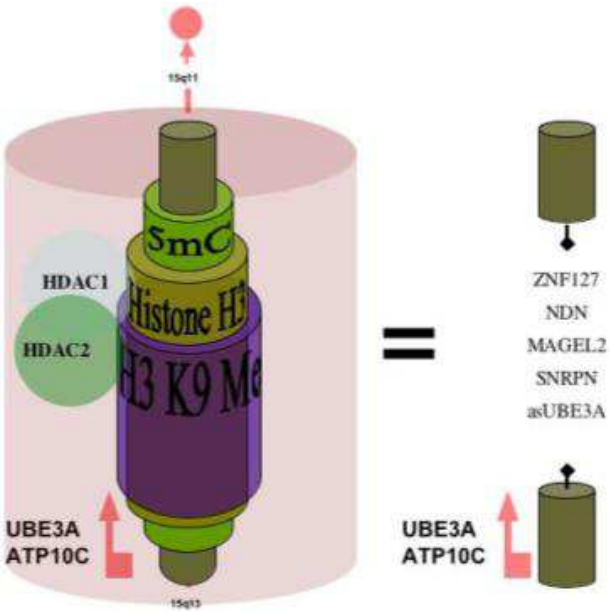



Figure 11: 15mat imprinted domain: Physical examination of the imprinted domain on maternally inherited chromosome 15 reveals DNA cytosine methylation, histone H3 tail methylation at lysine 9, recruitment of histone deacetylating enzymes, and deacetylated histones. These features are typical of closed, transcriptionally inactive chromatin, creating a functional knockout of multiple genes in the domain (center panel), including an antisense transcript to UBE3A. Silencing of asUBE3A permits expression of UBE3A from the maternally inherited chromosome.

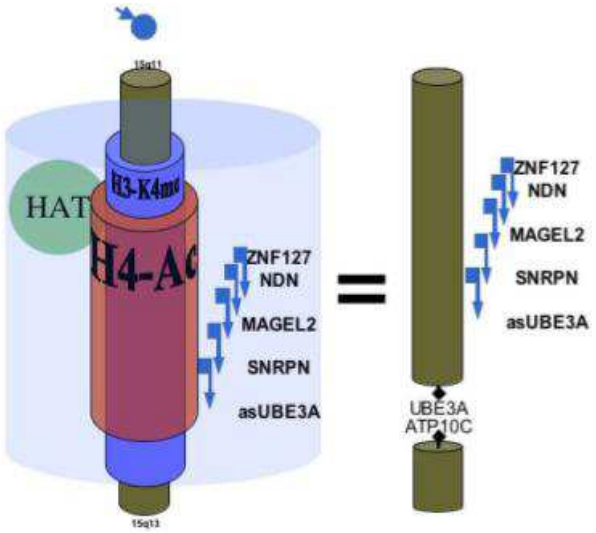



Figure 12: 15pat: The physical structure of the chromosome 15 PWS/AS domain inherited from the father is distinct from that from the mother. There is absent DNA cytosine 5-methylation, and tails of histones H3 and H4 are lysine 4-methylated and acetylated (H3-K4me and H4-Ac), respectively. There is recruitment of histone acetyltransferase (HAT) to the domain on the paternal chromosome. These features are typical of open, transcriptionally active chromatin. There is a "virtual" deletion of some genes in cis, including UBE3A and ATP10C.

## Life cycle of an imprinted gene

The behavior/expression of imprinted genes does not depend on the sex of the individual in which those genes reside, but on the sex of the parent from which the particular allele was inherited. In diploid somatic cells of an individual mammal, maternal and paternal alleles co-exist, but in the case of an imprinted gene, normally only one allele is functionally active. Propagation of this situation means that each DNA replication must be followed by self-templated imprint maintenance. The alternate stage in the life cycle of imprinted alleles occurs in the germ line. Here the imprints manifest in somatic cells are erased and an appropriate sperm-specific or egg-specific imprint is established on all gametic alleles, presumably by gonad-specific factors that reprogram the alleles. The testis-specific transcription factor BORIS regulates imprint establishment in the male germ line, while a female germ line specific imprint regulatory molecule has yet to be identified. When a new individual is generated by fusion of an egg and a sperm, the situation found in the parents is recreated. Thus, imprints cycle between periods of maintenance and establishment.

## Mendel, Lamarck, and epigenetic inheritance

Genomic imprinting represents a violation of Mendelian principles of inheritance, one of which stipulates that the dominance of one genetic allele over another is an inherent function of the alleles themselves, and does not depend upon the parent of origin of the allele. For example, Mendel observed the patterns of dominance and recessiveness for such traits as flower color and seed shape were independent of whether the dominant trait derived from pollen or ovum. Such observations may indicate a resistance of genetic alleles to environmental influences, such as the different climatic or cellular environments in which the male and female germ cells are propagated. While parental imprinting does not invalidate the results of Mendel's work, it does constitute a significant inheritance mechanism not observed by Mendel (Figure 6). By contrast, genomic imprinting provides positive evidence that genomes can show heritable functional plasticity dependent on allele environment; such a concept of genetic inheritance was favored by Lamarck and discredited through much of the Twentieth Century.

## Selection pressure for genomic imprinting

The consequences of imprinting are potentially disastrous since, for imprinted genes, animals have effectively abandoned the 'safety net' provided by diploidy and have shut-off a perfectly good gene copy. This drawback has spawned much philosophical debate over why imprinting could have possibly evolved, and furthermore, why it has been maintained throughout the mammalian radiation. One model proposes that imprinting evolved precisely to prevent parthenogenesis, and that the imprinting of a few loci is a small price to pay to guarantee functional diploidy in all other genes. A second model proposes that imprinting evolved as a consequence of the action of the host defense system against parasitic foreign DNA and that the presence of imprinted genes in mammalian genomes represents the shutting-off of "innocent by-standers". Note that these two models suggest that imprinting is an adaptive mechanism beneficial to the survival of the species. They also assign an

insignificant role to imprinting as a mechanism to control gene dosage. One prediction of the conflict hypothesis that - that imprinting is limited to viviparous animals - has been tested and the results support the hypothesis.

Probably the most widely accepted model of imprinting evolution is known as the conflict hypothesis (Haig and Graham, 1991; Moore and Haig, 1991). The conflict hypothesis views imprinting not as a beneficial adaptation of the species but as the deleterious consequence of a reproductive scenario involving polygamy, viviparity, and substantial maternal investments in the offspring, in the absence of a similar level of investment by the father. According to the conflict model, once viviparity arose among mammalian ancestors, natural selection acting upon asymmetric parental investments in diploid offspring operates on two conflicting strategies. On the one hand it is to the male's advantage that his offspring extract a maximum amount of nutrients from the mother, for he is unlikely to mate with that female again, and this should maximize his reproductive success and that of his offspring. On the other hand it is to the female's advantage to ration her investment in any given offspring, thereby conserving her resources for herself and her future offspring. According to the conflict hypothesis, therefore, imprinting arose due to a genetic tug-of-war between the parents that is played out in the offspring, through antagonistic efforts to control gene dosage.

Other predictions of this hypothesis are that imprinting occurs principally at fetal growth regulatory loci, that paternal epigenotypes drive expression of pro-growth genes while maternal epigenotypes suppress growth, and that such interparental conflicts exist especially under the reproductive physiology of viviparity.

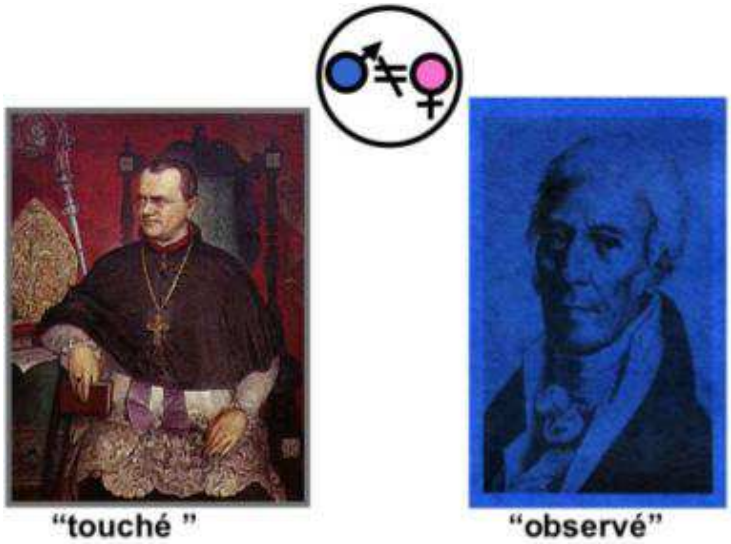



Figure 13: Genomic imprinting, in which some genetic traits are determined by the parent-specific germ cell milieu, violates Gregor Mendel's (left panel) principles of inheritance; by contrast imprinting supports, or at least takes the edge off some of the anathema heaped on Jean-Baptiste Lamarck's (right panel) concept of inheritance.


Figure 14: According the conflict hypothesis, genomic imprinting results from an interparental tug-of-war over the resources allocated the fetus by the mother during intrauterine gestation. The potential for conflicts between polygamous viviparous mammals is highlighted by the killing of lion young by non-paternal males (left). From the epigenomic perspective, the paternal epigenome can conflict with the maternal epigenome over offspring nutrient availability during intrauterine gestation Such conflicts are insufficient in oviparous animals such as monotreme mammals to drive the deleterious imprinted silencing of genes.

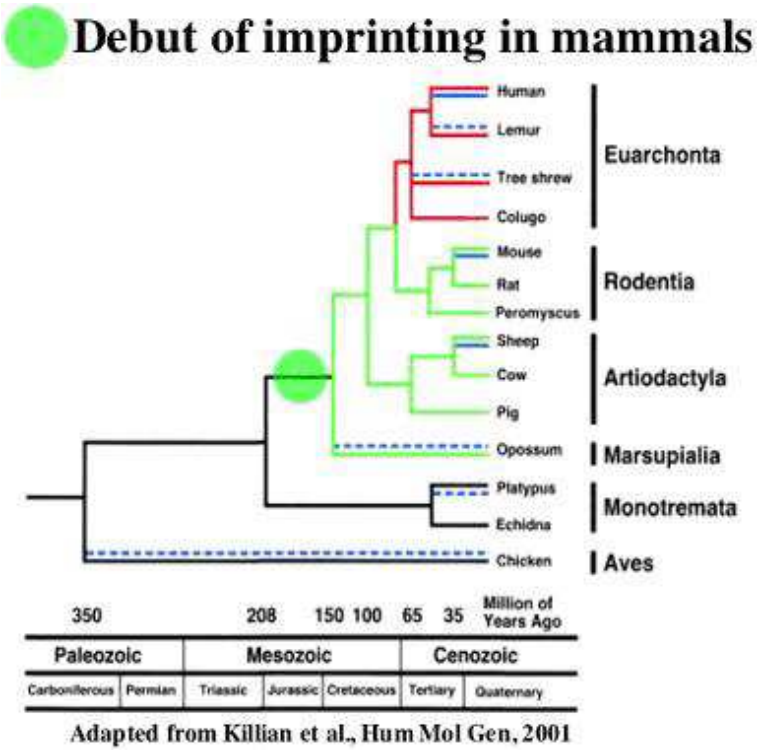



Figure 15: The phylogenetic distribution of genomic imprinting of IGF2R in birds, egg-laying mammals, marsupial mammals, and placental mammals (Killian et al., 2001). Black lines: not imprinted, ancestors not imprinted; green: imprinted, maternally expressed; red: imprinting lost. Blue lines refer to presence or absence (dashed) of putative IGF2R intron 2 imprint control element, for more information please see original paper.

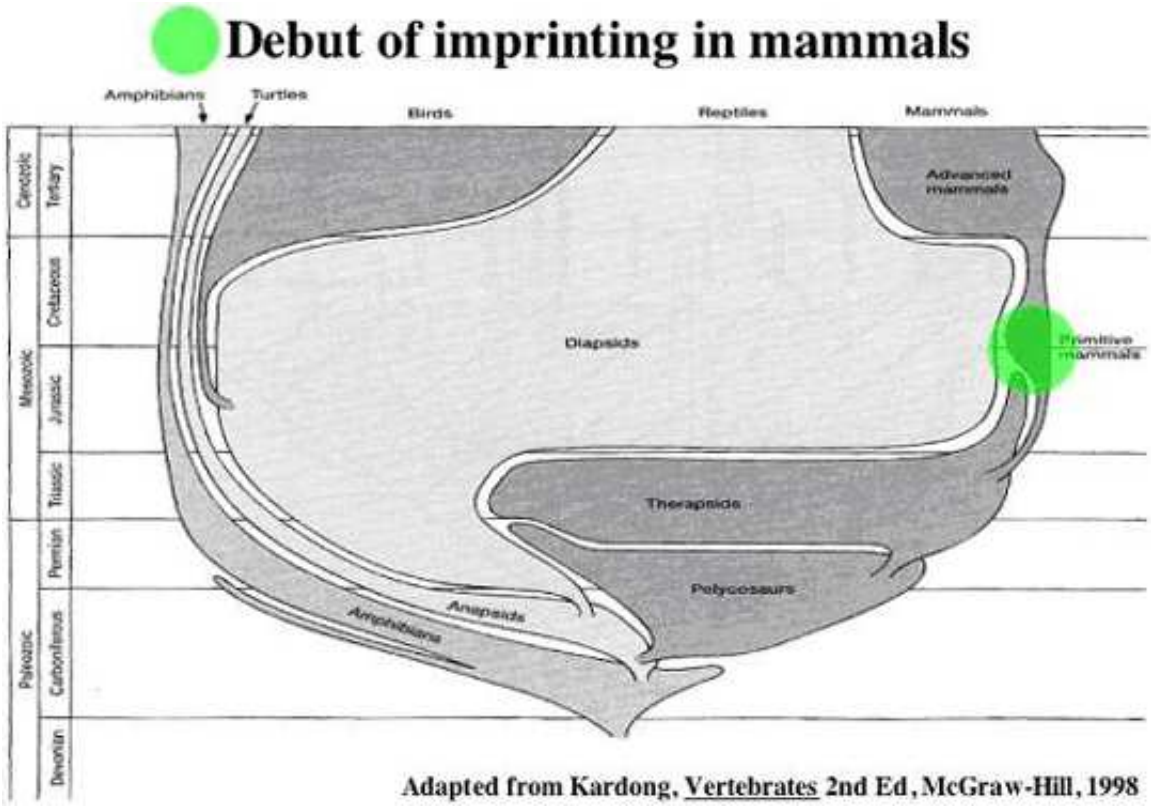



Figure 16: The potential roles of placentation and viviparity in the evolution of imprinting have been investigated through the phyloepigenetic analysis of IGF2 and M6P/IGF2R imprinting in birds, monotreme mammals, and marsupials. To date, genomic imprinting has only been demonstrated in viviparous mammals, supporting the conflict hypothesis.

### *Mules, hinnies, and George Washington*

Elucidating the phenomenon of imprinting has provided much insight into epigenetic regulation of development and cancer, but also helps explain centuries-old biological observations. Mule breeders 3 millennia ago observed that a horse mare crossed with a jack donkey yields a mule, whereas a horse stallion crossed with a jennet donkey produces a hinny, which has shorter ears, a thicker mane and tail, and stronger legs than the mule; thus indicating parental sex-dependent influence on phenotype. Although ancestral donkey crossers would likely have no problem with the concept and reality of parental genomic imprinting, imprinting more recently carries an iconoclastic aura, evidence of the powerful influence exerted by Gregor Mendel's writings; indeed, the phenomenon of imprinting has been classified within the realm of non-Mendelian genetics, as if Mendel's laws represent the Platonic ideal of genetic behavior.

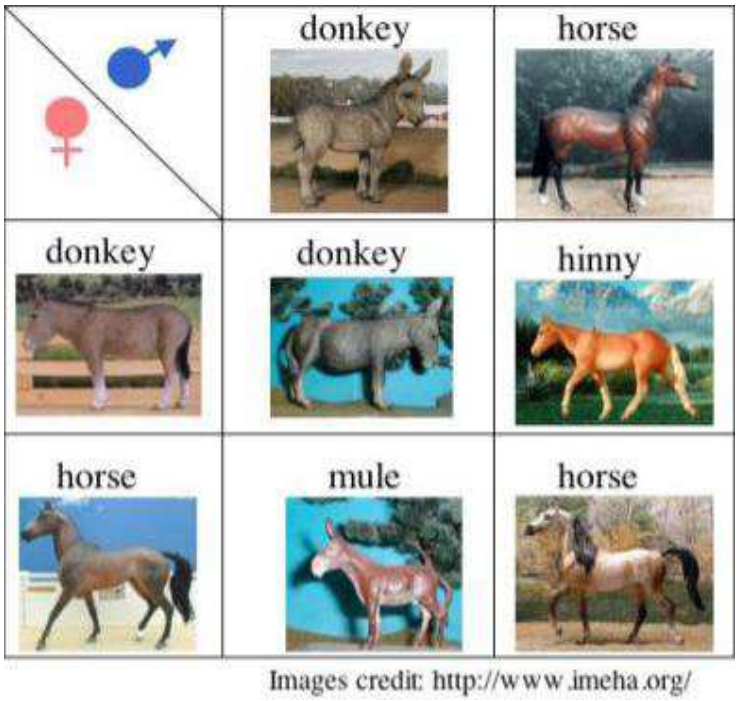



Figure 17: No hinnies in Washington. Following is an account of the origin of the mule industry in the United States, as per the archives of the U.S. Library of Congress. In the late Eighteenth Century there were no mules in the United States, but George Washington had become interested in them after learning of their unique attributes as work animals. The requisite male donkeys needed to breed mules must have also been scarce, for Spain had a virtual monopoly on the ass industry and it was illegal to export ass from the Spanish territories. Washington made an inquiry with the U.S. ambassador to Spain, and in 1785 King Charles III of Spain sent a large jack donkey to George Washington as a gift. The donkey was named "Royal Gift" and became the father of the mule industry in the U.S. It is interesting to note the male sex of the donkey sent to Washington, which is required in order to breed a true mule. Thus, technically speaking, because of genomic imprinting, there were no hinnies only mules in early Washington. Of course, female donkeys must have been eventually obtained in order to propagate a breeding donkey population.

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